(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 03/101980 A1

(51) International Patent Classification[7]: C07D 401/04, 405/14, A61K 31/53, C07D 405/12, 251/50, A61P 29/00

(21) International Application Number: PCT/EP03/50203

(22) International Filing Date: 28 May 2003 (28.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02077310.7 30 May 2002 (30.05.2002) EP

(71) Applicants *(for all designated States except US)*: **SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **ARQULE, INC** [US/US]; 19 Presidential Way, Woburn 01801 (US).

(71) Applicants and
(72) Inventors: **DEN HARTOG, Jacobus, A.J.** [NL/NL]; C. J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **REINDERS, Jan, H.** [NL/NL]; C. J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **VAN SCHARRENBURG, Guustaaf, J.M.** [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **PRAS-RAVES, Maria, L.** [NL/NL]; C. J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **GUSTAFSON, Gary, R.** [US/US]; 323 Springs Road, Bedford 01730 (US).

(74) Agent: **VERHAGE, Marinus**; C.J. Van Houtenlan 36, NL-1381 CP Weesp (NL).

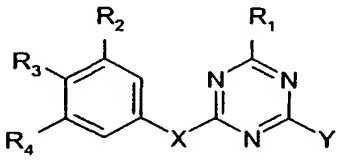
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

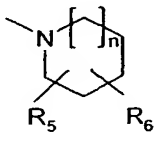
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

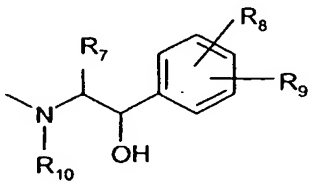
(54) Title: 1,3,5-TRIAZINE DERIVATIVES AS LIGANDS FOR HUMAN ADENOSINE-A3 RECEPTORS



(1)



(A)



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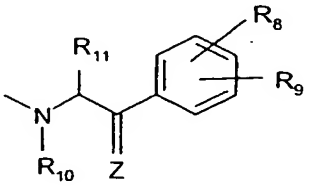

(C)

(57) Abstract: The invention relates to a group of novel triazine derivatives which are ligands for human adenosine-A3 receptors, as well as to pharmaceutical compositions containing a pharmacologically active amount of at least one of these compounds as an active ingredient. The invention relates to compounds of the general formula (1) wherein Y represents a group of the general formula (A), (B) or (C) and all other symbols have the meanings as given in the description.

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1,3,5-TRIAZINE DERIVATIVES AS LIGANDS FOR HUMAN ADENOSINE-A3 RECEPTORS

The present invention relates to a group of novel triazine derivatives which are ligands for human adenosine-A_3 receptors. The invention also relates to pharmaceutical compositions containing a pharmacologically active amount of at least one of these novel triazine derivatives as an active ingredient.

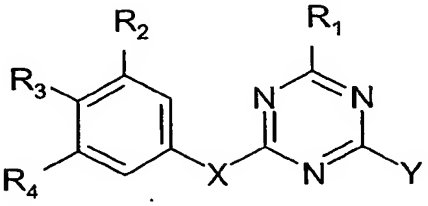
Caffeine and theophylline, two well known natural compounds, exert their pharmacological activities by interacting with adenosine receptors. This discovery had a major impact on adenosine receptor research. At present, four types of adenosine receptors have been identified and designated A_1, A_{2A}, A_{2B} and A_3 respectively. All four belong to the super-family of seven transmembrane G-protein coupled receptors. Adenosine receptors are ubiquitous and involved in a great variety of biological processes. Thus, during the past decades the therapeutic potential of adenosine receptor ligands has resulted in a substantial research interest. Recent reviews are: S. Hess, Recent advances in adenosine receptor antagonist research, Expert Opin. Ther. Patents, 11, 1547–1562, 2001, and M.A. Jacobson, Adenosine receptor agonists, Expert Opin. Ther. Patents, 12(4), 489-501, 2002.

Ligands for the various adenosine receptors are the subject of a large number of patent applications and patents. In only two of those triazines are described. WO 991163 describes a series of 2,4-bisphenyl substituted triazines showing nanomolar affinity for human adenosine-A_1 receptors.

The second patent application describing triazines, JP 11158073, is the closest prior art. It describes a series of substituted 1,3,5-triazines which are ligands for human adenosine-A_3 receptors, the most potent of which having affinities around 15 nM.

Surprisingly, it has now been found that in a series of triazine derivatives with novel combinations of substituents, a group of compounds was shown to have an affinity for human adenosine-A_3 receptors in the low nanomolar range.

The invention relates to compounds of the general formula (1)



(1)

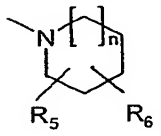
wherein:

R_1 represents halogen, alkyl(1-3C), O-alkyl(1-3C), CF_3, NH_2, N-(di)-alkyl(1-3C), N-(di)-alkenyl(1-3C), N-(di)-alkynyl(1-3C), N-alkyl(1-3C)alkenyl(1-3C), N-alkyl(1-3C)alkynyl(1-3C), N-alkenyl(1-3C)alkynyl(1-3C) or an optionally substituted C_2-C_8 cycloalkylamino group,

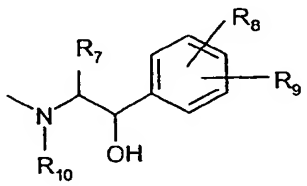
R_2, R_3 and R_4 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), phenoxy, hydroxyalkyl(1-3C), alkoxy(1-2C)-alkyl(1-2C), phenyl, N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, SO_2CH_3 or R_2 and R_3 together with the phenyl ring to which they are attached, represent an optionally substituted benzofuran, dihydrobenzofuran, benzodioxane, benzodioxolane or naphthalene ring system,

X represents NH, N-alkyl(1-3C), CH_2, O, S or a carbon-carbon bond,

Y represents a group of the general formula (A), (B) or (C):



(A)



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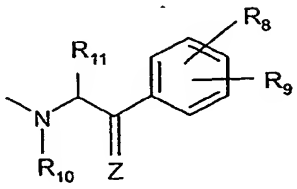


(C)

in which:

R_5 is either OH or CH_2OH

R_6 represents H, alkyl(1-3C), phenyl, NH_2, N-(di)-alkyl(1-3C), OH, O-alkyl(1-3C) or hydroxyalkyl(1-2C);

n has the value of 0, 1 or 2;

R_7 represents alkyl(1-3C), benzyl, hydroxyalkyl(1-2C) or methoxyalkyl(1-2C),

R_8 and R_9 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, or SO_2CH_3,

R_{10} represents H or alkyl(1-3C),

R_{11} represents H, alkyl(1-3C), benzyl, hydroxyalkyl(1-2C) or methoxyalkyl(1-2C),

Z represents NOH, NOalkyl(1-3C), O or S,

and pharmacologically acceptable salts thereof.

In the description of the substituents the abbreviation '**alkyl(1-3C)**' means 'methyl, ethyl,
n-propyl or isopropyl'.

In this specification '**C_2-C_8 cycloalkylamino**' means any cyclic amine containing from 2 to 8 carbons in the ring. The cycloalkylamino ring may contain other atoms and may be optionally substituted. Examples of C_2-C_8 cycloalkylamino include pyrrolidinyl, piperidinyl, morpholinyl, aziridinyl, pyrrolinyl and the like.

In this specification '**optionally substituted**' means that a group may or may not be further substituted by one or more groups selected from alkyl, alkenyl, alkynyl, aryl, fluoro, chloro, bromo, hydroxyl, alkyloxy, alkenyloxy, aryloxy, acyloxy, amino, alkylamino, dialkylamino, arylamino, thio, alkylthio, arylthio, cyano, oxo, nitro, acyl, amido, alkylamido, dialkylamido, carboxyl, or two optional substituents may together with the carbon atoms to which they are attached form a 5- or 6-membered aromatic or non-aromatic ring containing 0, 1 or 2 heteroatoms selected from nitrogen, oxygen

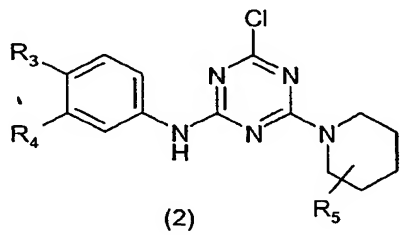
or sulphur. Optional substituents may themselves bear additional optional substituents. Preferred optional substituents include C_{1-3} alkyl such as for example methyl, ethyl, and trifluoromethyl, fluoro, chloro, bromo, hydroxyl, C_{1-3} alkyloxy such as for example methoxy, ethoxy and trifluoromethoxy, and amino.

All compounds having formula (1) in which the substituents on asymmetrical carbon atoms are in either the R-configuration or the S-configuration belong to the invention.

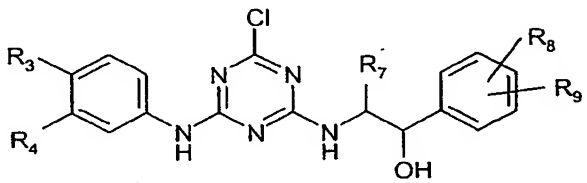
Also prodrugs, i.e. compounds which when administered to humans by any known route, are metabolized to compounds having formula (1), belong to the invention. In particular this relates to compounds with primary or secondary amino groups or hydroxy groups, a typical example being the compound with formula (9) and its enantiomers (see below). Such compounds can be reacted with organic acids to yield compounds which can be metabolized to compounds having formula (1).

The invention particularly relates to compounds having formula (1) wherein R_1 represents halogen, alkyl(1-3C), O-alkyl(1-3C), CF_3, NH_2 or N-(di)-alkyl(1-3C), and all other symbols have the meanings as given above.

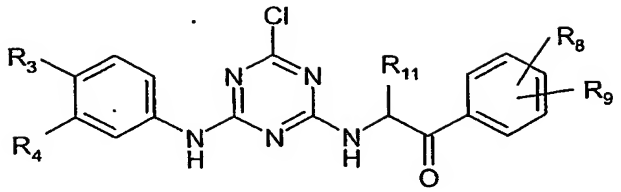
More particular the invention relates to compounds having formula (1) wherein R_1 = Cl, R_2 =H, X = NH, Y is either group (A), (B) or (C), R_6 = H, n=1, Z=O, R_{10}=H and R_3, R_4, R_5, R_7, R_8, R_9 and R_{11} have the meanings as described above, and including all possible stereo-isomers and prodrugs as outlined above, thus as represented by the general formulas (2), (3) and (4):



(2)

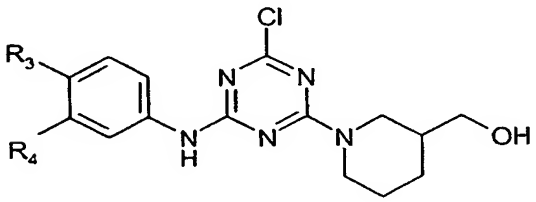


(3)

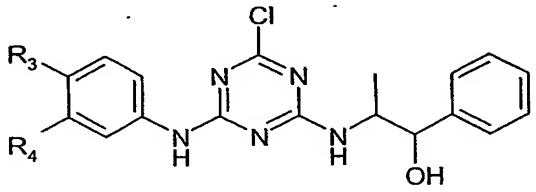


(4)

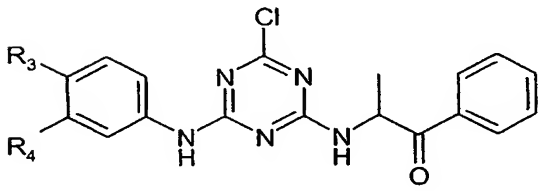
Yet more particular the invention relates to compounds of either formula (2), (3) or (4) in which R_5 = 3-CH_2OH; R_7 = CH_3; R_8 = H; R_9 = H; R_{11} = CH_3 and R_3 and R_4 have the meanings as described above, and including all possible stereo-isomers and prodrugs as outlined above, thus as represented by the general formulas (5), (6) and (7):



(5)

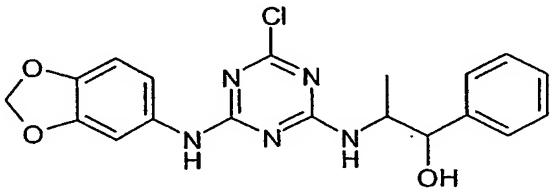


(6)



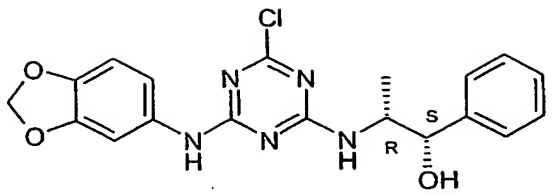
(7)

Even more preferred is the compound having formula (8) and its enantiomers.



(8)

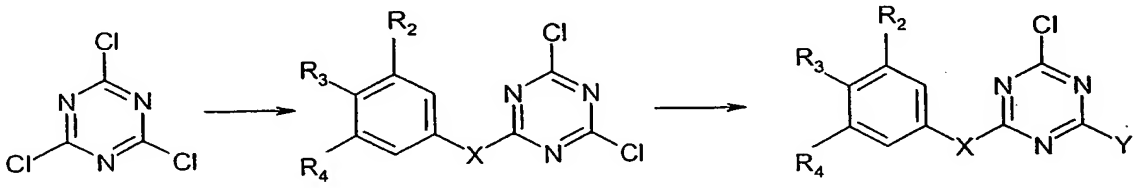
The best mode of the invention is the compound represented by formula (9):



(9)

This compound has an affinity for human adenosine-A_3 receptors of pK_i 9.0 $\pm$ 0.3.

The compounds of the invention and their salts can be obtained according to the general routes outlined below. Those with R_1 = Cl are synthesized according to scheme 1:



scheme 1

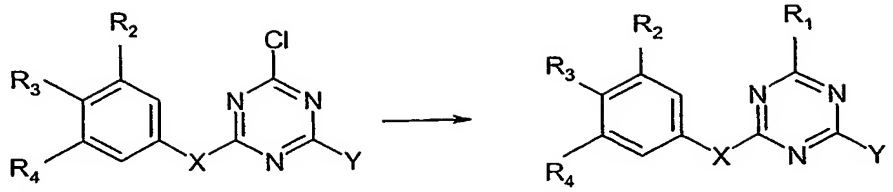
Experimental details for the first step in this general route are given in:

- J. Amer. Chem. Soc. 116, 1994, 4326 for X = NH;
- Chem. Pharm. Bull. 45, 1997, 291 for X = N-alkyl;
- Tetrahedron 56, 2000, 9705 for X = CH_2;
- Pol. J. Chem. 74, 2000, 837 for X = O;
- J Chem. Soc. C 1967, 466 for X = S, and in
- Tetrahedron 56, 2000, 9705 for X = carbon-carbon bond.

The compounds of the invention with R_1 = F or Br can be obtained fully analogously from the corresponding tri-halo derivatives. Experimental details are given in:

- J. Med Chem. 36 (26), 4195-4200, 1993 for R_1 is F, and in
- J. Prakt. Chem. 82, 536, 1910 for R_1 = Br.

The compounds of the invention with R_1 = O-alkyl(1-3C) or any of the amine substituents: NH_2, N-(di)-alkyl(1-3C), N-(di)-alkenyl(1-3C), N-(di)-alkynyl(1-3C), N-alkyl(1-3C)alkenyl(1-3C), N-alkyl(1-3C) alkynyl(1-3C), N-alkenyl(1-3C)alkynyl(1-3C) or an optionally substituted C_2-C_8 cycloalkylamino group, can be obtained by further substitution of the chloro-derivatives as outlined below in scheme 2:

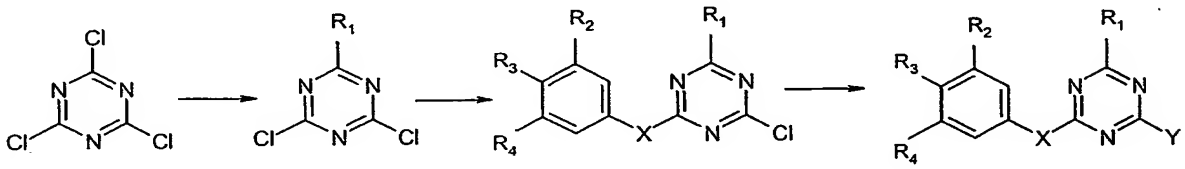


scheme 2

Experimental details are given in:

- Heterocycles 31 (5), 895-909, 1990 for R_1 = alkoxy, and in
- Tetrahedron, 54 (1998) 4051-4065 for R_1 = (substituted) amine.

Compounds of the invention with R_1 = alkyl(1-3C), CF_3 or iodine can be obtained by following the sequence of synthetic steps outlined below in Scheme 3.



Scheme 3

Experimental details are given in:

- J. Med Chem 42 (5), 805-818, 1999 for R_1 = alkyl,
- J. Chem Soc., Chem Comm 1988, (10) 638-639 for R_1 = CF_3, and in
- Eur. J. Org. Chem., 2002, 4181-4184 for R_1 = iodine

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid.

Suitable acid addition salts can be formed with inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid and nitric acid, or with organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, trifluoro acetic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene sulphonic acid.

The compounds of the invention of the general formula (1), as well as the salts thereof, have adenosine-A_3 (ant)agonistic activity. They are useful in the treatment of

disorders in which adenosine-A_3 receptors are involved, or that can be treated via manipulation of those receptors. For instance in: acute and chronic pain, inflammatory diseases including, arthritis, multiple sclerosis, asthma and psoriasis; gastro-intestinal disorders such as ulcers, inflammatory bowel disease (Crohn's disease) and ulcerative colitis; allergic responses such as eczema, atopic dermatitis and rhinitis; cardio-vascular disorders such as myocardial infarction, arrhythmias, hypertension, thrombosis, anaemia, arteriosclerosis, angina pectoris, cutaneous diseases such as urticaria, lupus erythematosus and pruritus; opthalmological disorders like glaucoma; respiratory disorders including chronic obstructive pulmonary disease, bronchitis and cystic fibrosis; central nervous system disorders including various forms of epilepsy, stroke, depression, sleep apnoea; disorders characterized by impairment of cognition and memory such as Alzheimer's disease, Creutzfeldt-Jacob disease, Huntington's disease, Parkinson's disease, neurorehabilitation (post-traumatic brain lesions); acute brain or spinal cord injury; diabetes, osteoporosis, diseases of the immune system, various carcinomas and leukemia, bacterial and viral infections.

The adenosine-A_3 receptor (ant)agonistic properties of the compounds of the invention were determined using the method outlined below.

Receptor Binding to human adenosine-A_3 receptors

Affinity of the compounds for human adenosine-A_3 receptors was determined using the receptor binding assay described by C.A. Salvatore et al.: Molecular cloning and characterization of the human A_3 adenosine receptor, Proc. Natl. Acad. Sci. USA, 90, 10365-10369, 1993. Briefly, membrane preparations were obtained from human recombinant (HEK 293) cells in which the human adenosine-A_3 receptor was stably expressed. Membranes were incubated at 22°C for 90 minutes with [^{125}I]-AB-MECA in the absence or presence of testcompounds in a concentration range from 10 µM down to 0.1 nM, diluted in a suitable buffer. Separation of bound radioactivity from free was done by filtration through Packard GF/B glass fiber filters with several washings with ice-cold buffer using a Packard cell harvester. Bound radioactivity was measured with a scintillation counter (Topcount, Packard) using a liquid scintillation cocktail (Microscint 0, Packard). Measured radioactivity was plotted against the concentration of the displacing test compound and displacement curves were calculated by four-parameter logistic regression, resulting in IC_{50} values, i.e. that

concentration of displacing compound by which 50% of the radioligand is displaced. Affinity pK_i values were calculated by correcting the IC_{50} values for radioligand concentration and its affinity for the human adenosine-A_3 receptor according to the Cheng-Prusoff equation:

$$pK_i = -\log (IC_{50} / (1+ S/K_d))$$

in which the IC_{50} is as described above, S is the concentration [^{125}I]-AB-MECA used in the assay expressed in mol/l (typically 0.1 nM), and K_d is the equilibrium dissociation constant of [^{125}I]-AB-MECA for human adenosine-A_3 receptors (0.22 nM).

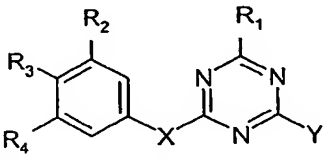
The compounds of the invention have a high affinity for adenosine-A_3 receptors in the binding assay described above. This property makes them useful in the treatment of disorders in which adenosine-A_3 receptors are involved, or that can be treated via manipulation of these receptors.

EXAMPLES

(1S,2R)-2-{[4-chloro-6-(3,4-methylenedioxy-phenylamino)-[1,3,5]triazin-2-yl]-amino}-1-phenyl-propan-1-ol

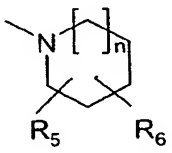
To a solution of cyanuric chloride (1.84 gr) in acetonitrile (20 ml), kept at a temperature of – 20°C under stirring, dropwise were subsequently added solutions of 3,4-methylenedioxy-aniline (1.37 gr) in acetonitrile (20 ml) and diisopropylethylamine (DIPEA) (1.29 gr) in acetonitrile (20 ml). After stirring at – 20°C for 1 hour, again dropwise were subsequently added solutions of DIPEA (1.29 gr) in acetonitrile (20 ml) and (1S,2R)-(+)-norephedrine (1.51 gr) in acetonitrile (20 ml). The mixture was allowed to warm to room temperature and was stirred for another 2 hours. The resulting reaction mixture was concentrated in vacuo. After addition of ethylacetate (250 ml) the organic layer was subsequently washed with a solution of HCl in water (1M, 100ml) , a solution of NaOH in water (1M, 100 ml) and brine (50 ml). The organic layer was dried over sodiumsulphate, filtered and concentrated in vacuo. The resulting product was purified by column chromatography using silicagel and a mixture of heptane: ethylacetate (3:1) as the eluent. The resulting pure product (formula (9), see above, example B-44, see table) was obtained as a white solid in 80 % yield.

The invention is further illustrated by means of the following specific examples listed in the tables below and represented by the general formula:

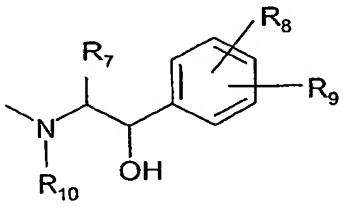


(1)

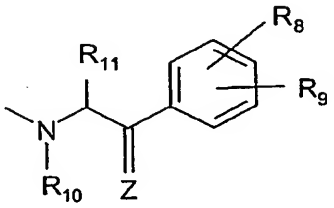
wherein Y represents a group of the general formula (A), (B) or (C):



(A)



(B)



(C)

These examples are only intended to further illustrate the invention in more detail, and therefore are not deemed to restrict the scope of the invention in any way.

nr	R_1	X	R_2	R_3	R_4	Y	n	R_5	R_6
A-1	Cl	NH	H	H	H	(A)	1	3-CH_2OH	H
A-2	Cl	NH	OCH_3	H	H	(A)	1	3-CH_2OH	H
A-3	Cl	NH	OCH_3	H	H	(A)	1	3-CH_2OH	4-CH_3
A-4	Cl	NH	OCH_3	H	H	(A)	1	3-CH_2OH	4-phenyl
A-5	Cl	NH	OCH_3	H	H	(A)	1	3-CH_2OH	4-$N(CH_3)_2$
A-6	Cl	NH	OCH_3	H	H	(A)	1	3-CH_2OH	5-CH_2OH
A-7	Cl	NH	H	OCH_3	H	(A)	1	3-CH_2OH	H
A-8	Cl	NH	CH_3	H	H	(A)	1	3-CH_2OH	H
A-9	Cl	NH	Cl	H	H	(A)	1	3-CH_2OH	H
A-10	Cl	NH	OC_2H_5	H	H	(A)	1	3-CH_2OH	H
A-11	Cl	NH	H	OC_2H_5	H	(A)	1	3-CH_2OH	H
A-12	Cl	NH	$CH(OH)CH_3$	H	H	(A)	1	3-CH_2OH	H
A-13	Cl	NH	H	1-morpholinyl	H	(A)	1	3-CH_2OH	H
A-14	Cl	NH	CH_3	CH_3	H	(A)	1	3-CH_2OH	H
A-15	Cl	NH	F	CH_3	H	(A)	1	3-CH_2OH	H
A-16	Cl	NH	F	OCH_3	H	(A)	1	3-CH_2OH	H
A-17	Cl	NH	OCH_3	H	CF_3	(A)	1	3-CH_2OH	H
A-18	Cl	NH	OCH_3	H	OCH_3	(A)	1	3-CH_2OH	H
A-19	Cl	NH	-phenyl-		H	(A)	1	3-CH_2OH	H
A-20	Cl	NH	-O-CH_2-O-		H	(A)	1	3-OH	H
A-21	Cl	NH	-O-CH_2-O-		H	(A)	1	4-OH	H
A-22	Cl	NH	-O-CH_2-O-		H	(A)	1	4-OH	4-phenyl
A-23	Cl	NH	H	H	H	(A)	1	4-OH	H
A-24	Cl	NH	H	CH_3	H	(A)	1	4-OH	H
A-25	Cl	NH	Cl	H	H	(A)	1	4-OH	H
A-26	Cl	NH	OCH_3	H	H	(A)	1	4-OH	H
A-27	Cl	NH	H	OCH_3	H	(A)	1	4-OH	H
A-28	Cl	NH	OC_2H_5	H	H	(A)	1	4-OH	H
A-29	Cl	NH	H	OC_2H_5	H	(A)	1	4-OH	H
A-30	Cl	NH	H	$(CH_2)_2OH$	H	(A)	1	4-OH	H

nr	R_1	X	R_2	R_3	R_4	Y	n	R_5	R_6
A-31	Cl	NH	O-phenyl	H	H	(A)	1	4-OH	H
A-32	Cl	NH	H	O-phenyl	H	(A)	1	4-OH	H
A-33	Cl	NH	H	1-morpholinyl	H	(A)	1	4-OH	H
A-34	Cl	NH	CH_3	CH_3	H	(A)	1	4-OH	H
A-35	Cl	NH	F	CH_3	H	(A)	1	4-OH	H
A-36	Cl	NH	F	OCH_3	H	(A)	1	4-OH	H
A-37	Cl	NH	OCH_3	H	CF_3	(A)	1	4-OH	H
A-38	Cl	NH	OCH_3	H	OCH_3	(A)	1	4-OH	H
A-39	Cl	NH	-phenyl-		H	(A)	1	4-OH	H
A-40	Cl	NH	$-O-CH_2-O-$		H	(A)	1	2-CH_2OH	H
A-41	Cl	NH	OCH_3	H	H	(A)	1	2-CH_2OH	H
A-42	Cl	NH	H	OCH_3	H	(A)	1	2-CH_2OH	H
A-43	Cl	NH	H	OC_2H_5	H	(A)	1	2-CH_2OH	H
A-44	Cl	NH	H	1-morpholinyl	H	(A)	1	2-CH_2OH	H
A-45	Cl	NH	CH_3	CH_3	H	(A)	1	2-CH_2OH	H
A-46	Cl	NH	F	OCH_3	H	(A)	1	2-CH_2OH	H
A-47	Cl	NH	OCH_3	H	OCH_3	(A)	1	2-CH_2OH	H
A-48	Cl	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-49	CH_3	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-50	OCH_3	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-51	1-morpholinyl	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-52	1-pyrrolidinyl	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-53	NH-propargyl	NH	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-54	Cl	NCH_3	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-55	Cl	O	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-56	Cl	S	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-57	Cl	CH_2	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-58	Cl	bond	$-O-CH_2-O-$		H	(A)	1	3-CH_2OH	H
A-59	Cl	NH	$-O-CH_2-O-$		H	(A)	1	4-CH_2OH	H
A-60	Cl	NH	$-O-CH_2-O-$		H	(A)	0	3-OH	H
A-61	Cl	NH	CH_3	H	H	(A)	0	3-OH	H

nr	R_1	X	R_2	R_3	R_4	Y	n	R_5	R_6
A-62	Cl	NH	Cl	H	H	(A)	0	3-OH	H
A-63	Cl	NH	OCH_3	H	H	(A)	0	3-OH	H
A-64	Cl	NH	H	OCH_3	H	(A)	0	3-OH	H
A-65	Cl	NH	H	OC_2H_5	H	(A)	0	3-OH	H
A-66	Cl	NH	H	1-morpholinyl	H	(A)	0	3-OH	H
A-67	Cl	NH	CH_3	CH_3	H	(A)	0	3-OH	H
A-68	Cl	NH	F	CH_3	H	(A)	0	3-OH	H
A-69	Cl	NH	F	OCH_3	H	(A)	0	3-OH	H
A-70	Cl	NH	-phenyl-		H	(A)	0	3-OH	H
A-71	Cl	NH	-O-CH_2-O-		H	(A)	0	3-CH_2OH	H

nr	R_1	X	R_2	R_3	R_4	Y	R_7	R_8	R_9	R_{10}	stereo
B-1	Cl	NH	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-2	Cl	NH	H	H	H	(B)	CH_3	H	H	H	1R,2S
B-3	Cl	NCH_3	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-4	Cl	O	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-5	Cl	CH_2	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-6	Cl	S	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-7	Cl	bond	H	H	H	(B)	CH_3	H	H	H	1S,2R
B-8	Cl	NH	H	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-9	Cl	NH	OCH_3	H	H	(B)	CH_3	H	H	H	1S,2R
B-10	Cl	NH	OCH_3	H	H	(B)	CH_3	H	H	H	1R,2S
B-11	Cl	NH	OCH_3	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-12	Cl	NH	OCH_3	H	H	(B)	CH_2CH_3	H	H	H	1S,2R
B-13	Cl	NH	OCH_3	H	H	(B)	$(CH_2)_2CH_3$	H	H	H	1S,2R
B-14	Cl	NH	OCH_3	H	H	(B)	CH_2-phenyl	H	H	H	1S,2R
B-15	Cl	NH	OCH_3	H	H	(B)	CH_2OH	H	H	H	1S,2R
B-16	Cl	NH	OCH_2CH_3	H	H	(B)	CH_3	H	H	H	1S,2R
B-17	Cl	NH	OCH_2CH_3	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-18	Cl	NH	CH_3	H	H	(B)	CH_3	H	H	H	1S,2R
B-19	Cl	NH	Cl	H	H	(B)	CH_3	H	H	H	1S,2R
B-20	Cl	NH	Cl	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-21	Cl	NH	$CH(OH)CH_3$	H	H	(B)	CH_3	H	H	H	1S,2R
B-22	Cl	NH	$CH(OH)CH_3$	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-23	Cl	NH	O-phenyl	H	H	(B)	CH_3	H	H	H	1S,2R
B-24	Cl	NH	O-phenyl	H	H	(B)	CH_3	H	H	CH_3	1R,2R
B-25	Cl	NH	H	OCH_3	H	(B)	CH_3	H	H	H	1S,2R
B-26	Cl	NH	H	OCH_3	H	(B)	CH_3	H	H	H	1R,2S
B-27	Cl	NH	H	OCH_3	H	(B)	CH_3	H	H	CH_3	1R,2R
B-28	Cl	NH	H	OCH_2CH_3	H	(B)	CH_3	H	H	H	1S,2R
B-29	Cl	NH	H	1-morpholinyl	H	(B)	CH_3	H	H	H	1S,2R
B-30	Cl	NH	H	CH_3	H	(B)	CH_3	H	H	H	1S,2R

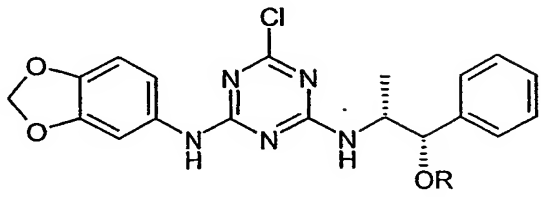
Nr	R_1	X	R_2	R_3	R_4	Y	R_7	R_8	R_9	R_{10}	stereo
B-31	Cl	NH	H	CF_3	H	(B)	CH_3	H	H	H	1S,2R
B-32	Cl	NH	H	O-phenyl	H	(B)	CH_3	H	H	H	1S,2R
B-33	Cl	NH	H	O-phenyl	H	(B)	CH_3	H	H	CH_3	1R,2R
B-34	Cl	NH	H	$(CH_2)_2OH$	H	(B)	CH_3	H	H	CH_3	1R,2R
B-35	Cl	NH	F	CH_3	H	(B)	CH_3	H	H	H	1S,2R
B-36	Cl	NH	F	OCH_3	H	(B)	CH_3	H	H	H	1S,2R
B-37	Cl	NH	F	OCH_3	H	(B)	CH_3	H	H	CH_3	1R,2R
B-38	Cl	NH	F	OCH_3	H	(B)	CH_3	H	H	CH_3	1R,2S
B-39	Cl	NH	OCH_3	H	CF_3	(B)	CH_3	H	H	H	1S,2R
B-40	Cl	NH	OCH_3	H	OCH_3	(B)	CH_3	H	H	H	1S,2R
B-41	Cl	NH	OCH_3	H	OCH_3	(B)	CH_3	H	H	CH_3	1R,2R
B-42	Cl	NH	CH_3	CH_3	H	(B)	CH_3	H	H	H	1S,2R
B-43	Cl	NH	-phenyl-		H	(B)	CH_3	H	H	H	1S,2R
B-44	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-45	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1R,2S
B-46	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	CH_3	1S,2R
B-47	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	CH_3	1S,2S
B-48	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	CH_3	1R,2S
B-49	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	CH_3	1R,2R
B-50	Cl	NCH_3	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-51	Cl	O	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-52	Cl	S	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-53	Cl	CH_2	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-54	Cl	bond	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R
B-55	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	3-OH	H	H	1R,2S
B-56	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	4-OH	H	H	1S,2R
B-57	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	3-OH	4-OH	H	1R,2S
B-58	Cl	NH	$-O-CH_2-O-$		H	(B)	CH_3	$2-OCH_3$	$5-OCH_3$	H	*racemic*
B-59	NH_2	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1R,2S
B-60	$N(CH_3)_2$	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1R,2S
B-61	1-pyrrolidinyl	NH	$-O-CH_2-O-$		H	(B)	CH_3	H	H	H	1S,2R

Nr	R_1	X	R_2	R_3	R_4	Y	R_7	R_8	R_9	R_{10}	stereo
B-62	1-morpholinyl	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R
B-63	1-piperidinyl	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R
B-64	NH-propargyl	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R
B-65	N(CH_3)propargyl	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R
B-66	CH_3	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R
B-67	OCH_3	NH	-O-CH_2-O-		H	(B)	CH_3	H	H	H	1S,2R

Nr	R_1	X	R_2	R_3	R_4	Y	R_8	R_9	R_{10}	R_{11}	Z
C-1	Cl	NH	-O-CH_2O-		H	(C)	H	H	H	H	O
C-2	Cl	NH	-O-CH_2O-		H	(C)	H	H	H	CH_3	O
C-3	CH_3	NH	-O-CH_2O-		H	(C)	H	H	H	CH_3	O
C-4	OCH_3	NH	-O-CH_2O-		H	(C)	H	H	H	CH_3	O
C-5	Cl	NH	OCH_3	H	H	(C)	H	H	H	CH_3	O
C-6	Cl	NH	H	OCH_3	H	(C)	H	H	H	CH_3	O
C-7	Cl	NH	-O-CH_2O-		H	(C)	H	H	H	CH_3	N-OH
C-8	Cl	NH	-O-CH_2O-		H	(C)	H	H	H	CH_3	N-OCH_3
C-9	Cl	NH	-O-CH_2O-		H	(C)	H	H	H	H	N-OH
C-10	Cl	NH	OCH_3	H	H	(C)	H	H	H	H	N-OH
C-11	Cl	NH	H	OCH_3	H	(C)	H	H	H	H	N-OH

EXAMPLES OF PRODRUGS

To illustrate the concept 'prodrugs' the following compounds with the general formula (10) have been prepared:



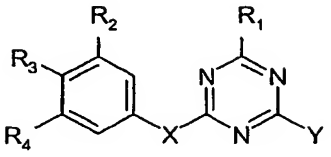
(10)

example	R-group
Pro-1	propionyl
Pro-2	pivaloyl
Pro-3	nicotinoyl
Pro-4	N-acetyl-isonipecotyl
Pro-5	methoxyacetyl
Pro-6	acethoxyacetyl
Pro-7	nonaoyl

Prodrugs having formula (10) have no affinity for human adenosine-A3 receptors, but after hydrolysis they generate the compound with formula (9) (see above) which is highly active.

Claims

1. Compounds of the general formula (1)



(1)

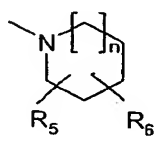
wherein:

R_1 represents halogen, alkyl(1-3C), O-alkyl(1-3C), CF_3, NH_2, N-(di)-alkyl(1-3C), N-(di)-alkenyl(1-3C), N-(di)-alkynyl(1-3C), N-alkyl(1-3C)alkenyl(1-3C), N-alkyl(1-3C)alkynyl(1-3C), N-alkenyl(1-3C)alkynyl(1-3C) or an optionally substituted C_2-C_8 cycloalkylamino group,

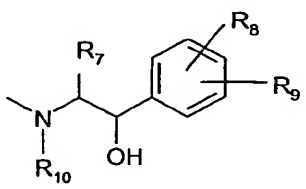
R_2, R_3 and R_4 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), phenoxy, hydroxyalkyl(1-3C), alkoxy(1-2C)-alkyl(1-2C), phenyl, N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, SO_2CH_3 or R_2 and R_3 together with the phenyl ring to which they are attached, represent an optionally substituted benzofuran, dihydrobenzofuran, benzodioxane, benzodioxolane or naphthalene ring system,

X represents NH, N-alkyl(1-3C), CH_2, O, S or a carbon-carbon bond,

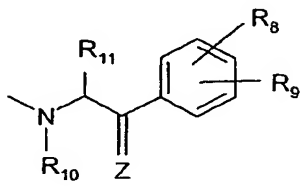
Y represents a group of the general formula (A), (B) or (C):



(A)



(B)



(C)

in which:

R_5 is either OH or CH_2OH

R_6 represents H, alkyl(1-3C), phenyl, NH_2, N-(di)-alkyl(1-3C), OH, O-alkyl(1-3C) or hydroxyalkyl(1-2C);

n has the value of 0, 1 or 2;

R_7 represents alkyl(1-3C), benzyl, hydroxyalkyl(1-2C) or methoxyalkyl(1-2C),

R_8 and R_9 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, or SO_2CH_3,

R_{10} represents H or alkyl(1-3C),

R_{11} represents H, alkyl(1-3C), benzyl, hydroxyalkyl(1-2C) or methoxyalkyl(1-2C),

Z represents NOH, NOalkyl(1-3C), O or S,

pharmacologically acceptable salts thereof, and all compounds having formula (1) in which the substituents on potentially asymmetrical carbon atoms are in either the R-configuration or the S-configuration, as well as prodrugs thereof.

2. Compounds as claimed in claim 1 of the general formula (1) wherein R_1 represents halogen, alkyl(1-3C), O-alkyl(1-3C), CF_3, NH_2 or N-(di)-alkyl(1-3C); R_2, R_3 and R_4 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), phenyl, N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, SO_2CH_3, or R_2 and R_3 together with the phenyl ring to which they are attached, represent a benzofuran, benzodioxane, or benzodioxolane ring system, X repre-sents NH, N-alkyl(1-3C), CH_2, O, S or a carbon-carbon bond, Y represents a group of the general formula (A) or (B), in which R_5 is either OH or CH_2OH; R_6 represents H, alkyl(1-3C), phenyl, NH_2, N-(di)-alkyl(1-3C), OH, O-alkyl(1-3C) or hydroxyalkyl

(1-2C); n has the value of 0, 1 or 2; R_7 represents alkyl(1-3C), benzyl or hydroxyalkyl(1-2C); R_8 and R_9 independently represent H, halogen, alkyl(1-3C), CF_3, OH, O-alkyl(1-3C), N-(di)-alkyl(1-3C), 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, OCF_3, SCH_3, $SOCH_3$, or SO_2CH_3; and R_{10} =H

3. Compounds as claimed in claim 1 of the general formula (1) wherein Y is a group of the general formula (A) and R_1, R_2, R_3, R_4, R_5, R_6, X and n have the meanings as in claim 1.

4. Compounds as claimed in claim 1 of the general formula (1) wherein Y is a group of the general formula (A) and R_1, R_2, R_3, R_4, R_5, R_6, X and n have the meanings as in claim 2.

5. Compounds as claimed in claim 1 of the general formula (1) wherein Y is a group of the general formula (B) and R_1, R_2, R_3, R_4, R_7, R_8, R_9, R_{10} and X have the meanings as in claim 1.

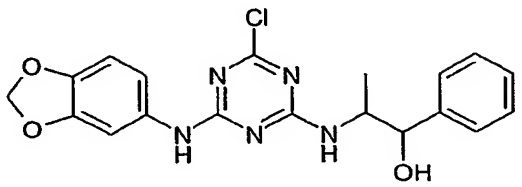
6. Compounds as claimed in claim 1 of the general formula (1) wherein Y is a group of the general formula (B) and R_1, R_2, R_3, R_4, R_7, R_8, R_9, R_{10} and X have the meanings as in claim 2.

7. Compounds as claimed in claim 1 of the general formula (1) wherein Y is a group of the general formula (C) and R_1, R_2, R_3, R_4, R_8, R_9, R_{10}, R_{11}, X and Z have the meanings as in claim 1.

8. Compounds as claimed in claim 1 having formula (1) wherein R_1 = Cl, R_2 =H, X=NH, Y is either group (A), (B) or (C), R_6 = H, n=1, Z=O, R_{10}=H and R_3, R_4, R_5, R_7, R_8, R_9 and R_{11} have the meanings as in claim 1

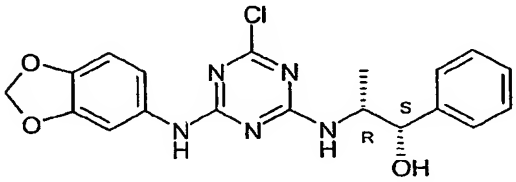
9. Compounds as claimed in claim 1 having formula (1) wherein R_1 = Cl, R_2 =H, X=NH, Y is either group (A), (B) or (C), R_5 = 3-CH_2OH, R_6 = H, n=1, R_7 = CH_3;
R_8 = H; R_9 = H, Z=O, R_{10}=H, R_{11} = CH_3 and R_3 and R_4, have the meanings as in claim 1

10. Compound as claimed in claim 1 having formula (8) and enantiomers thereof:



(8)

11. Compound as claimed in claim 1 having formula (9)



(9)

12. Pharmaceutical compositions containing a pharmacologically active amount of at least one of the compounds as claimed in one of the claims 1-11 as an active ingredient,

13. Use of a compound as claimed in one of the claims 1-11 for the preparation of a pharmaceutical composition for the treatment of disorders in which adenosine-A_3 receptors are involved, or that can be treated via manipulation of those receptors,

14. Use as claimed in claim 13 characterized in that said disorders are acute and chronic pain, inflammatory diseases including, arthritis, multiple sclerosis, asthma and psoriasis; gastro-intestinal disorders such as ulcers, inflammatory bowel disease (Crohn's disease) and ulcerative colitis; allergic responses such as eczema, atopic dermatitis and rhinitis; cardio-vascular disorders such as myocardial infarction, arrhythmias, hypertension, thrombosis, anaemia, arteriosclerosis, angina pectoris, cutaneous diseases such as urticaria, lupus erythematosus and pruritus; opthalmological disorders like glaucoma; respiratory disorders including chronic obstructive pulmonary disease, bronchitis and cystic fibrosis; central nervous system disorders including various forms of epilepsy, stroke, depression, sleep apnoea; disorders characterized by impairment of cognition and memory such as Alzheimer's disease, Creutzfeldt-Jacob disease, Huntington's

disease, Parkinson's disease, neurorehabilitation (post-traumatic brain lesions); acute brain or spinal cord injury; diabetes, osteoporosis, diseases of the immune system, various carcinomas and leukemia, bacterial and viral infections.

5

INTERNATIONAL SEARCH REPORT

Internati[redacted] Application No
PCT/EP 03/50203

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D405/14 A61K31/53 C07D405/12 C07D251/50
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 11 158073 A (TAKEDA CHEM IND LTD) 15 June 1999 (1999-06-15) cited in the application claim 1	1,9
A	WO 99 11633 A (BOEHRINGER INGELHEIM PHARMA ;POHL GERALD (DE); GAIDA WOLFGANG (DE)) 11 March 1999 (1999-03-11) cited in the application claim 1; table 7	1,9

☐ Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2003	30/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/50203

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11158073 A	15-06-1999	NONE	
WO 9911633 A	11-03-1999	DE 19735800 A1	25-02-1999
		WO 9911633 A1	11-03-1999